REMARKS/ARGUMENTS

Claims 1-11 and 16-18 have been canceled. Claims 12-15 are pending in the instant application. In view of the examiner's earlier restriction requirement, applicant retains the right to present claims 1-11 and 16-18 in a divisional application.

Applicants acknowledge that any objection or rejection of record not expressly repeated in the current Office Action dated August 17, 2004 have been overcome by the Applicant's response and are withdrawn.

Claim Rejections – 35 USC § 102

The Examiner maintains the rejection under 35 U.S.C. 102(b) as being anticipated by Spencer et al. (WO 98/42361).

The Examiner maintains the argument that Spencer et al. teaches GH administration for an erectile dysfunction disorder as a result of aging and the Examiner asserts that decreased GH is a result of aging. The Examiner further argues that the limitation of claim 12 that there is "insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists" is met by Spencer in teaching administration of GH for a disorder as a result of aging since decreased GH occurs with aging.

The present invention relates to the surprising finding that there is a casual connection between increased GH levels with sexual stimulation and the resulting penile erection. Spencer teaches GH treatment for the regeneration of severed or damaged parasympathetic nerves that regulate erectile function (Abstract; page 2, lines 14-16; page 2, lines 27-30; page 4, lines 26-29; page 6, lines 20-22). The applicants do not find any teaching in Spencer that

GH level deficiences are associated with severed or damaged parasympathetic nerves. The Examiner argues that growth hormone deficiency and aging are concomitant. Even though aging may result in decreased levels of GH there is no teaching in Spencer that there is a lack of increase in GH during sexual stimulation in the elderly let alone any patient suffering from an erectile dysfunction. The prior art, including Spencer, teach away from using GH to treat sexual dysfunction. Spencer states: *GH has been reported to be ineffective in impotence and to produce erectile insufficiency (Ra et al. J. of Urology 156, p522 1996)* (page 4, lines 23-26). Furthermore, Ra et al concludes; *we have demonstrated potent action of PRL and GH in* ***causing*** *cavernous smooth muscle contraction and* ***inhibiting penile erection****.* (page 10, last paragraph – emphasis added). In relying upon the theory of inherency, the Examiner **must** provide a basis in fact and/or technical reasoning to reasonably support the position that the alleged inherency necessarily flows from the teachings of the applied prior art. It is respectfully submitted that the Examiner has failed to provide either a basis in fact or technical reasoning to support the argument of inherency. The present work is the first positive connection between sexual stimulation, increase in GH levels, and penile erection.

Applicant requests that Final Rejection be withdrawn and a timely Notice of Allowance be issued in this case.

Respectfully submitted,

By__________________________

S. Christopher Bauer
Reg. No. 42,305
314-274-6257

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In Vitro Contraction of the Canine Corpus Cavernosum Penis by Direct Perfusion with Prolactin or Growth Hormone

[Investigative Urology]

Ra, Shibun; Aoki, Hikaru; Fujioka, Tomoaki; Sato, Fumio; Kubo, Takashi; Yasuda, Naoki

From the Second Department of Physiology and the Department of Urology, Iwate Medical University, School of Medicine, Morioka, Iwate, Japan Accepted for publication January 19, 1996. (H. Oaki) Requests for reprints: Department of Urology, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020, Japan.

Outline

Graphics

Abstract

Purpose: It is well established that hyperprolactinemia, most typically seen in prolactinoma patients, causes hypogonadism and impotence. There seem to be a good possibility that hyperprolactinemia causes impotence, at least partially via some intrinsic property of prolactin (PRL), rather than through its suppressive effects on the hypothalamic-pituitary-gonadal testosterone dynamics. In the present investigation, we used an in vitro canine model to attempt

to clarify whether direct action of PRL on the corpus cavernosum penis may lead to erectile insufficiency. Growth hormone (GH) and placental lactogen (PL), both having close structural and functional homologies to PRL, were also studied.

Materials and Methods: Isometric tension measurement with cavernous strips was performed in the presence or absence of 10 sup -5 to 10 sup -9 M. PRL, GH, or PL in the perfusion medium. The tension change induced by the test substances was normalized relative to that induced by 120 mEq KCl.

Results: Both PRL and GH produced dose-related elevations (p less than 0.01) of the cavernous tension, whereas PL and thiol-cleaved PRL in comparable doses were without effect (p greater than 0.05). When the tension rise produced by 120 mEq KCl was taken as 100 percent, the maximum contractions produced by PRL and GH were 80 percent and 110 percent. The minimum effective concentration was 10 sup -8 to 10 sup -7 M. for both PRL and GH. Pretreatment with indomethacin (10 sup -5 M.), but not tetrodotoxin (10 sup -5 M.), partially suppressed (p less than 0.05) the effects of PRL.

Conclusion: These results suggest that PRL and GH directly and specifically produced contraction of the corpus cavernosum penis, resulting in erectile insufficiency, and that the effect of PRL is partially mediated by prostaglandin.

Key Words: penile erection, prostaglandins, prolactin, somatotropin

It has been well established that hyperprolactinemic states in man, typically seen in patients with prolactinoma, are associated with hypogonadism and impotence. [1,2] Although documented by the impairment of nocturnal penile tumescence (NPT), [3] is likely to be due to organic rather than psychogenic causes, the exact site and mode of action of prolactin (PRL) continues to be controversial. Proposals have been made that excess PRL acts at multiple levels within the hypothalamic-pituitary-gonadal axis to suppress serum testosterone concentration. [4,5] However, testosterone replacement alone does not usually improve potency in hyperprolactinemic patients. Normalization of excess PRL appears to be essential for the reversal of impotence, although there is a subset of patients in whom normalization of both PRL and testosterone is required before impotence can be corrected. [1] Therefore, it may reasonably be speculated that PRL suppresses erectile function through mechanisms that are at least partially independent of testosterone. The site(s) or mechanism(s) of such independent action of PRL has been only poorly understood, although there has been a proposal that PRL acts centrally on the dopaminergic pathway in the preoptic area. [6]

In our recent report, we showed in vivo in the dog that an excess concentration of PRL, when injected directly into the corpus cavernosum penis, was capable of attenuating or abolishing the penile erectile response induced by electrical stimulation of the pelvic splanchnic nerve. [7] These results clearly indicated a direct action of excess PRL on the corpus cavernosum penis to cause erectile insufficiency, although such a mechanism of PRL-induced impotence has not been given much consideration in the past. In the present communication was extended these in vivo observations to in vitro studies to further confirm the direct action of PRL in the penile corpus cavernosum. Growth hormone (GH) and placental lactogen (PL), both having quite similar molecular structures and functional homologies to PRL, were also studied.

Materials and Methods

Preparation of in vitro cavernous model

Adult male mongrel dogs weighing 8 to 15 kg. were used. After induction of anesthesia with ketamine chloride (15 mg/kg. intramuscularly), sodium thiopental in 45 to 60 mg. intravenous boluses was given as needed to maintain an adequate level of anesthesia during surgery. The entire penis was excised and the corpora cavernosa were dissected free from the tunica albuginea. Test procedures were performed with one corpus cavernosum, and the other received control procedures where appropriate. Each strip from the right or left corpus cavernosum measuring approximately 2 X 2 X 6 mm. was submerged in a 5-ml. organ chamber containing Krebs-Ringer solution and gassed with 95 percent O_2 and 5 percent CO_2 (pH 7.4, 37C). One end of each strip was fixed in a vertical alignment with silk ties to a metallic support on the bottom of the chamber and the other end to a silk tie connected to a force transducer for isometric tension measurement.

Initial tension of the strip was set at 3 g., and the system was allowed to equilibrate for 2 hours. The basal tension at the end of the 2-hour period was usually about 2 g. Repetitive challenges with KCl (120 mEq) solution were used to test the contractile capacity of each strip. Only those specimens that gave reproducible responses to repeated KCl challenge were used in subsequent experiments. When the magnitude of the potassium-induced contraction reached a steady state, the system was considered optimal. After an adequate stabilization with repeated KCl challenges, the cavernous strip was washed with perfusion medium to remove KCl from the system in preparation for actual experiments.

Administration of PRL, GH, and PL. Ovine PRL, porcine GH, human PL and human serum albumin (HSA) were all purchased from Sigma Chemical Co., St. Louis, Missouri (#L6520, #S8648, #L4759, #A1653). Tetrodotoxin and indomethacin were also obtained from Sigma (#T5651, #I7378). All test substances used were dissolved with the perfusion medium and given in a volume of 0.2 to 0.5 ml. The dosage of each test substance was expressed as the calculated concentration in the chamber after administration. The degree of contraction induced by each test substance was expressed relative to that by 120mEq KCl. Thiol-cleaved PRL was prepared by sequential treatment with dithiothreitol (DTT) and iodoacetamide (IAc). [8] Prolactin in 0.06 N Tris-HCl buffer (pH 8.6) was incubated with 10 mM. DTT for 45 minutes in the dark. Iodoacetamide was then added at 50 mM., followed by another 45-minute incubation in the dark. Both incubations were carried out at room temperature. After incubation, the sample was filtered through a membrane (Centricone, Amicon, Beverly, Massachusetts, cut-off 10,000) to remove excess reagents. The control PRL sample was processed similarly except that it was not incubated with DTT and IAc.

Results

Effects of varying concentrations of native or disulfide-cleaved PRL on cavernous tension.

After equilibration by potassium challenge, graded doses of PRL were sequentially added to the chamber in order of increasing concentration. After each increment of the PRL dose, cavernous tension was allowed to rise and reach the maximum attainable plateau before adding the next dose. Such experiments were repeated with a total of 31 cavernous strips. As shown in Figure 1, a stepwise increase of the cavernous tension was observed after each increment of PRL dose beyond 10 sup -8 M. The minimum effective dose was 10 sup -8 M. and the maximum dose was 10 sup -6 M. Figure 2. Human serum albumin tested as a control substance showed no effects

on the cavernous tension Figure 2. When the intramolecular disulfide bonds were irreversibly disrupted by DTT/IAc, PRL no longer produced contraction of the cavernous strip, affording specificity to the effect of the native PRL Figure 3.

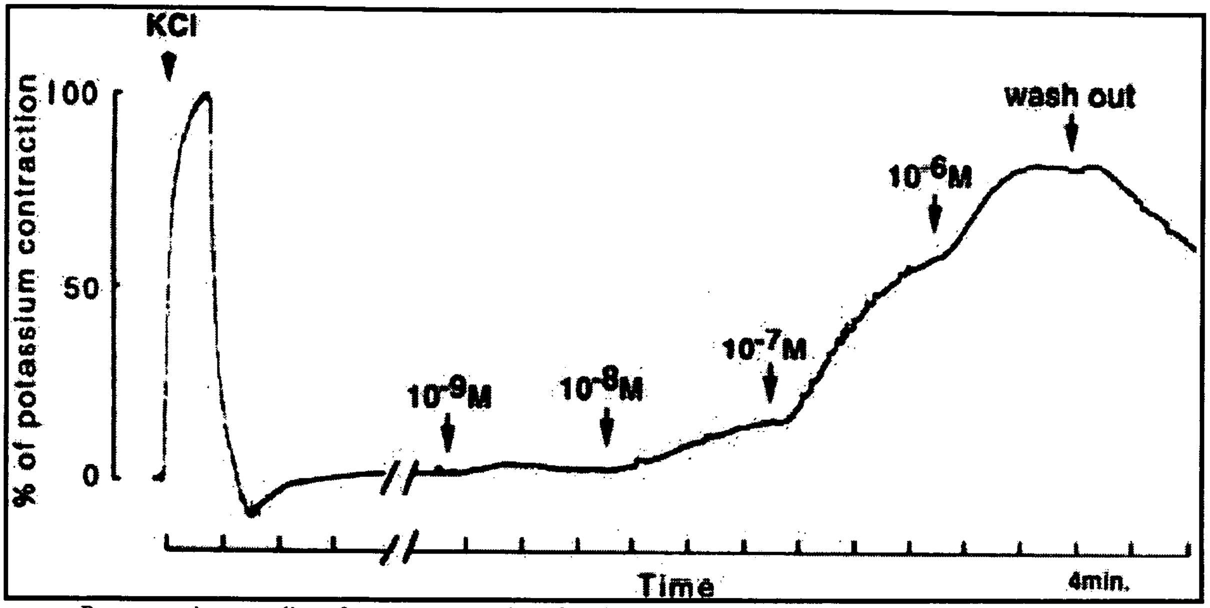

Figure 1. Representative recording of percent contraction of canine cavernous strip in response to sequential administration of increasing doses (10 sup -9 to 10 sup -6 M.) of PRL. Cavernous contraction induced by 120 mEq KCl is taken as 100 percent.

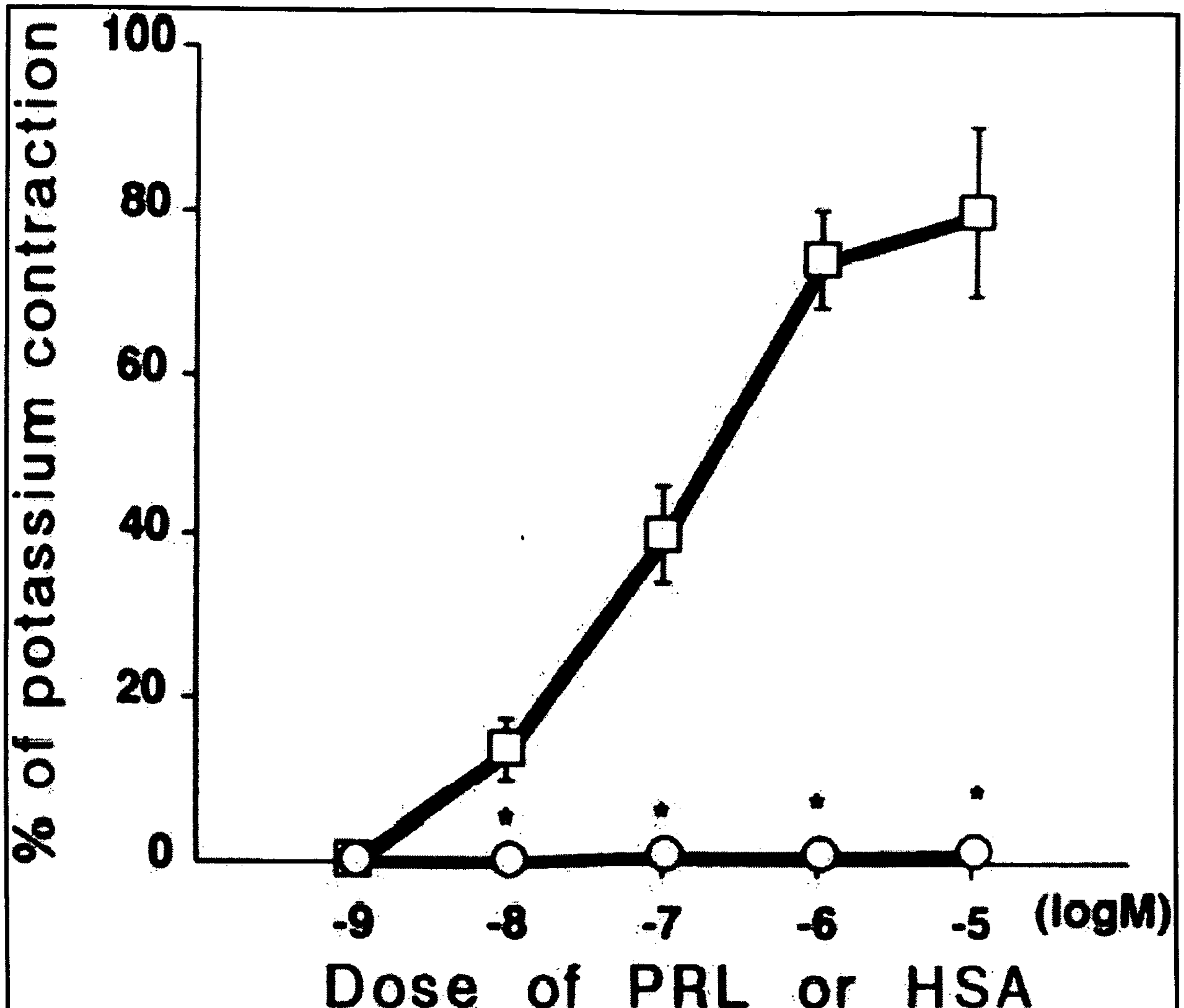

Figure 2. Percent contraction of canine cavernous strip in response to graded doses of PRL (squares) or HSA (circles). Cavernous contraction induced by 120 mEq KCl is taken as 100 percent. Mean and standard error of mean from 31 strips (PRL) and 6 strips (HSA) are shown. * p less than 0.01 compared with corresponding doses of PRL.

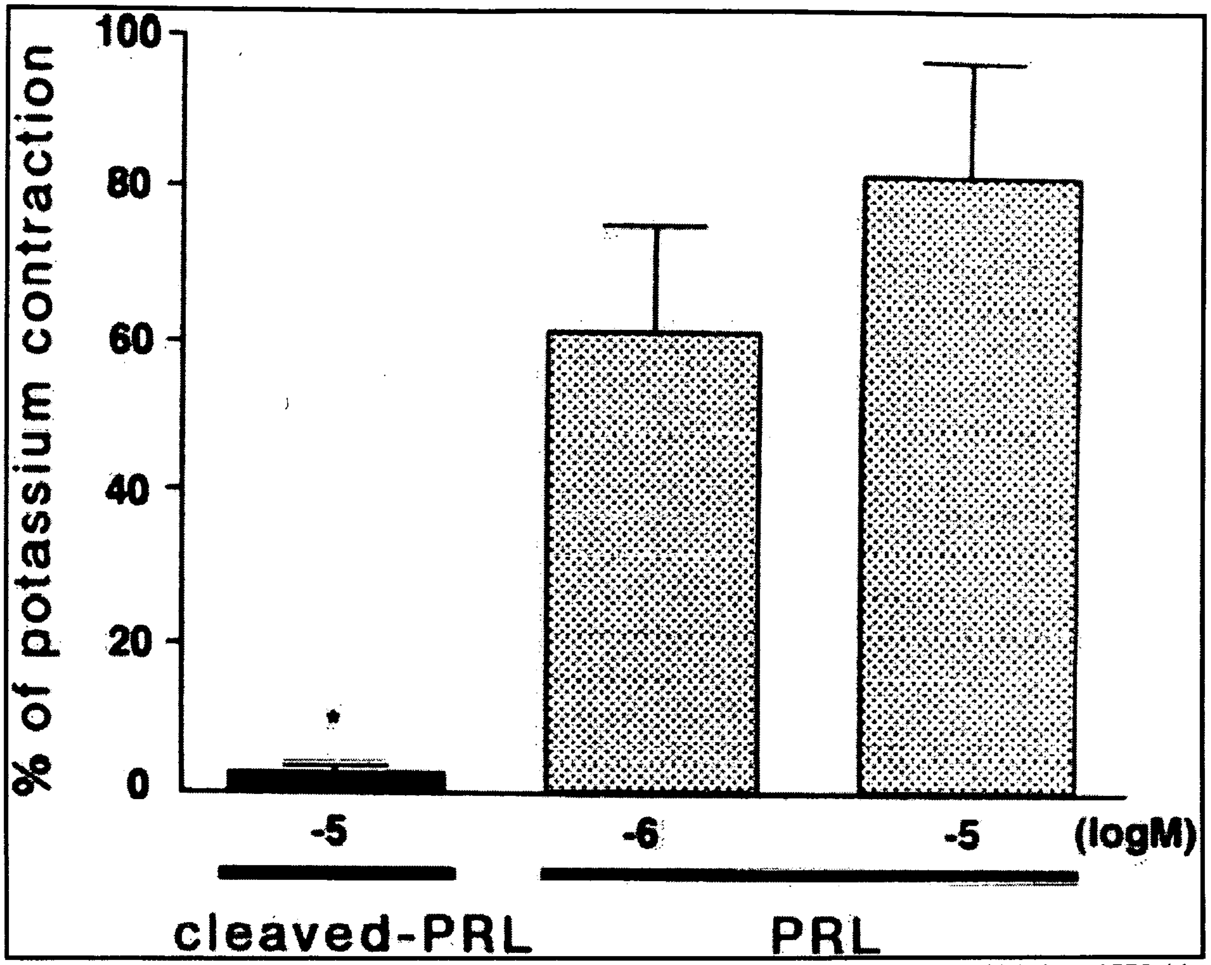

Figure 3. Percent contraction of canine cavernous strip in response to indicated doses of native PRL or thiol-cleaved PRL (cleaved-PRL). Mean and standard error of mean from 8 strips are shown for each group. * p less than 0.05 compared with corresponding dose of native PRL.

Effects of indomethacin or tetrodotoxin on PRL-induced cavernous contraction.

Cavernous strips were pretreated for 10 minutes with either 10 sup -5 M. indomethacin, 10 sup -5 M. tetrodotoxin, or perfusion medium alone before PRL was added to the system. As shown in Figure 4, indomethacin, a prostanoid synthesis inhibitor, caused significant (p less than 0.01) suppression of PRL-induced cavernous contraction at PRL doses of 10 sup -6 and 10 sup -5 M., but not 10 sup -7 M. In contrast, tetrodotoxin, a sodium channel blocker, caused no significant suppression at all tested doses Table 1.

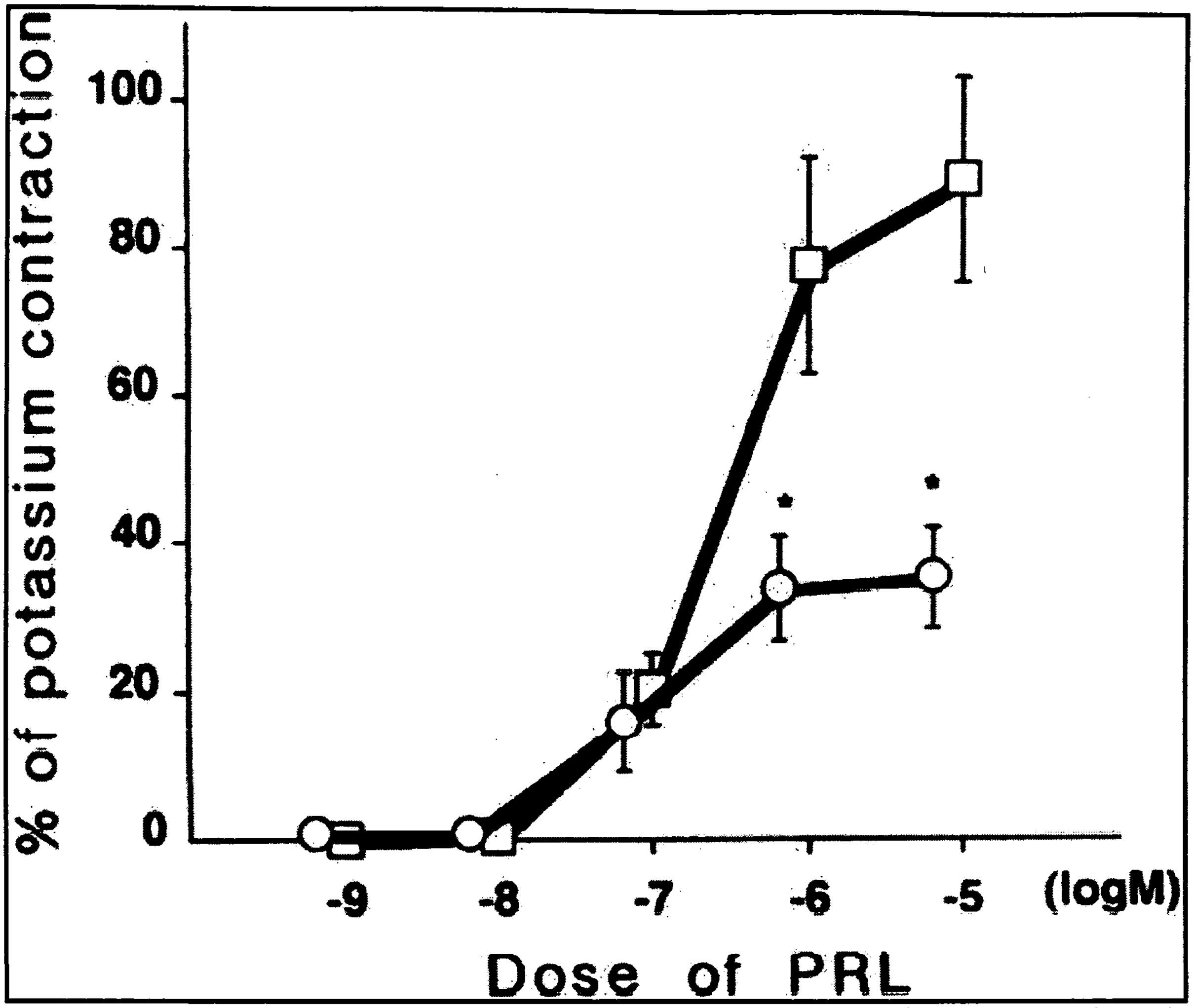

Figure 4. Percent contraction of canine cavernous strip in response to graded doses of PRL with (circles) or without (squares) pretreatment with 10 sup -5 M. indomethacin. Mean and standard error of mean from 5 strips are shown for each group. * p less than 0.01 compared with controls without indomethacin pretreatment.

	Dose of PRL (M.)		
	10^{-7}	10^{-6}	10^{-5}
Control	40.6 ± 5.9	74.6 ± 6.1	80.7 ± 10.5
TTX	18.2 ± 8.4	69.5 ± 12.4	82.2 ± 11.4

Mean and standard error of the mean from 6 strips are shown for each group. There were no significant differences ($p > 0.05$) between the 2 experimental groups.

Table 1. Percent contraction of the canine cavernous strip in response to the indicated doses of PRL with or without pretreatment with 10 sup -5 M. tetrodotoxin (TTX).

Effects of varying concentrations of GH or PL on the cavernous tension.

After equilibration using potassium challenges, graded doses of GH or PL were sequentially added to the chamber in order of increasing concentration. After each increment of the GH or PL dose, cavernous tension was allowed to rise and reach the maximum attainable plateau before addition of the next dose. Such experiments were repeated 5 times for both GH and PL, with

different cavernous strips. As shown in Figure 5, a stepwise increase of the cavernous tension was observed after 10 sup -8 to 10 sup -6 M. GH. The dose-response relationship for GH was roughly comparable to that for PRL Figure 6. In contrast, PL was entirely devoid of such activity Figure 6.

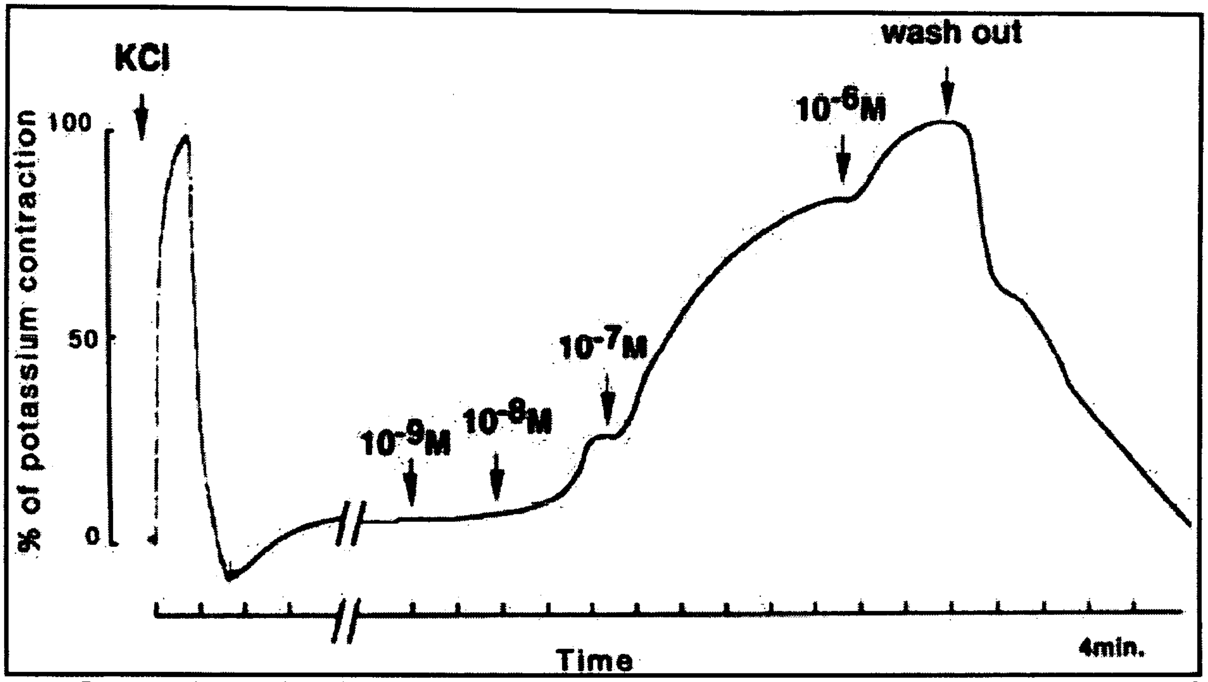

Figure 5. Representative recording of percent contraction of canine cavernous strip in response to sequential administration of increasing doses (10 sup -9 to 10 sup -6 M.) of GH. Cavernous contraction induced by 120 mEq KCl is taken as 100 percent.

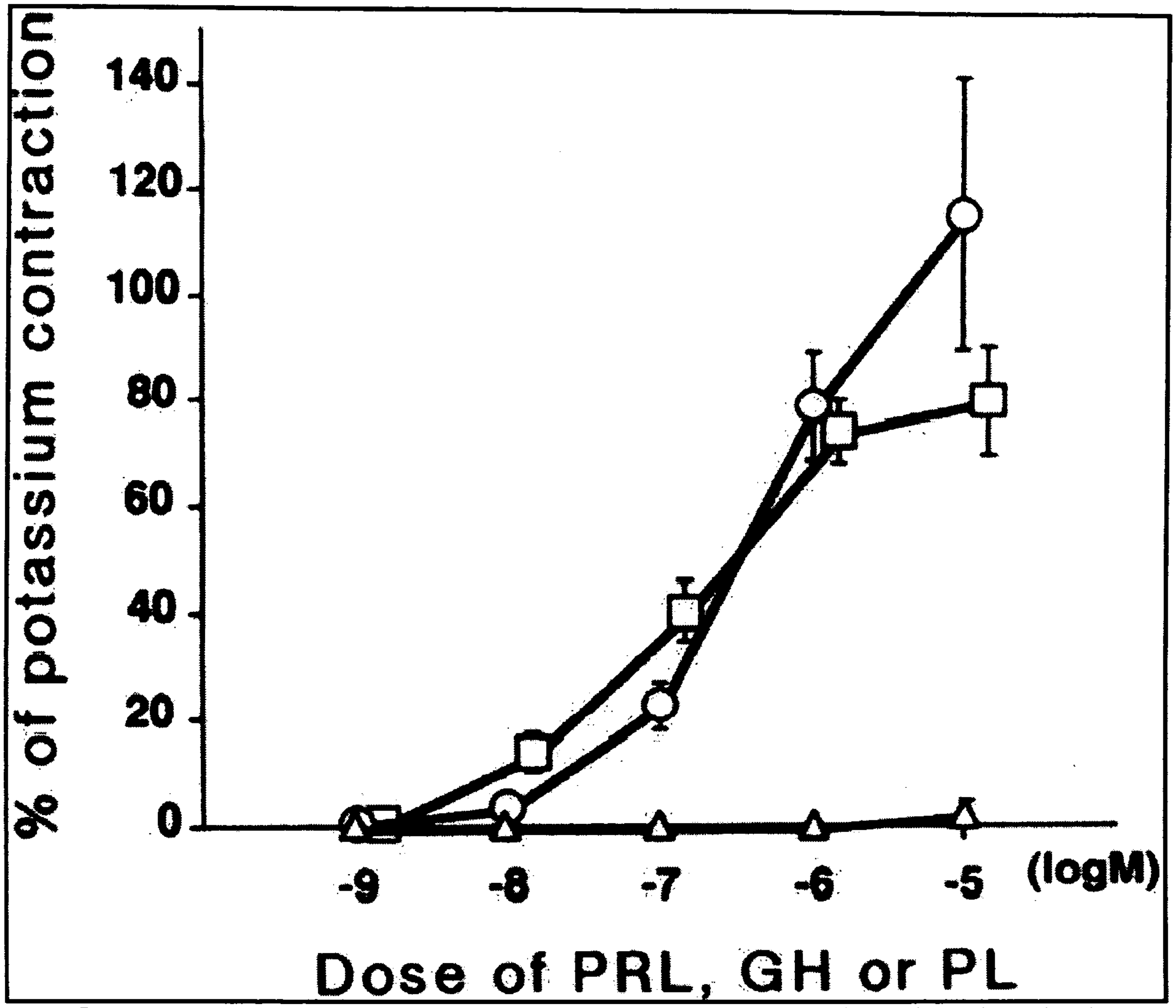

Figure 6. Percent contraction of canine cavernous strip in response to graded doses of PRL (squares), GH (circles) or PL (triangles). Same data as in Figure 2 are plotted for PRL for comparison. Cavernous contraction induced by 120 mEq KCl is taken as 100 percent. Mean and standard error of mean from 31 strips (PRL), 5 strips (GH) and 5 strips (PL) are shown. Good responses were obtained with GH, but PL elicited no appreciable responses. Magnitude of responses did not differ (p greater than 0.05) between PRL and GH groups.

Discussion

Our results indicate that local perfusion of PRL consistently produced an intense contraction of the cavernous tissues in the dog, and that tetrodotoxin failed to alter this in vitro effect of PRL. This suggests that PRL acts directly on the corpus cavernosum penis and that its effect is not neurally mediated. Furthermore, this effect of PRL was partially but significantly suppressed by indomethacin, a specific inhibitor of prostaglandin synthesis, which suggests a mediation by prostaglandin of the PRL effect. Since the cavernous tissues we used were not stripped of the sinusoidal endothelial cells, our data do not differentiate between the endothelial cells and the smooth muscle cells as the primary site of PRL action. Thus PRL may act directly on the smooth muscle cells, where it stimulates generation of prostaglandin, or it may act primarily on the endothelial cells, and prostaglandin liberated from the endothelial cells acts on the smooth muscles to cause their contraction.

In general, PRL receptors have been widely demonstrated in the male reproductive organs including the prostate, testis, epididymis and seminal vesicle. [9] However, only very limited information is available as to whether PRL receptors exist in the penile corpus cavernosum.

Although PRL receptors could not be demonstrated in the rat's "penis" in the report by Ouhtit et al., [10] it is unclear whether these authors specifically examined the corpus cavernosum penis in the absence of detailed description on the experimental methods. Although our current results favor the presence of a specific class of PRL receptor in this tissue, further investigation is clearly needed for a more definitive answer. Our results also indicate that the disruption of the molecular integrity of PRL by disulfide cleavage with combined treatments with DTT and IAc caused a complete disappearance of the PRL effect in the cavernous tissue. This would suggest that the PRL effect we found required some specific molecular interactions in the target tissue and is not a nonspecific effect. The specificity of the PRL effect was further reinforced by the absence of cavernous contraction when PL or HSA was tested. Thus, current in vitro results agree quite well with our previously reported in vivo studies, [7] both demonstrating an intense cavernous contraction or inhibition of cavernous relaxation by PRL.

It is indeed intriguing that GH was as potent as PRL in producing the cavernous contraction, whereas PL, structurally very similar to GH, was totally devoid of such activity. These discrepant results might be explained by the close functional homology demonstrated between PRL and GH receptors [9,11] and the relative independence between the PRL and PL receptors. [12] In fact we cannot rule out the possibility that PRL and GH share their receptors in the cavernous tissue with considerable cross-binding, analogous to the shared use of PRL receptor in the mammary gland. Whether specific receptors for GH exist in the cavernous tissue is unknown. Since the effects of PRL or GH in the cavernous tissue appear to be rather profound, it may well be that the impotence seen clinically in prolactinoma patients or acromegalics can be partially accounted for on this basis, although it certainly does not exclude additional sites and/or modes for the action of these hormones. Since serum PRL is elevated in approximately 50 percent of acromegalic cases, impotence in these patients may be caused by excess of either PRL or GH, or both. The serum PRL levels of the patients with prolactinoma or serum GH levels of acromegalics reported in the literature range from 78 ng./ml. to 40 microgram/ml. or from 5 to 541 ng./ml., respectively. [13,14] The minimum effective concentration in our current studies was approximately 200 ng./ml. for both PRL and GH, which falls well within these ranges, although it certainly is higher than the serum GH concentrations commonly encountered in average acromegalics.

Certain factors need to be taken into account when considering the effective concentrations of PRL or GH. In our experiments the cavernous tissue was exposed to a high level of these hormones for only a brief period whereas in patients with prolactinoma or in acromegalics, exposure to excess concentrations usually extends for a long period of time before impotence becomes evident. Furthermore our experimental designs involved a heterologous system in which we tested the effect of ovine PRL or porcine GH in the canine corpus cavernosum penis. Although we found that human PRL was also effective in the canine tissue (unpublished observation), there may be some quantitative differences in the effectiveness of PRL or GH of a given species depending upon whether the test system is homologous or heterologous. Taking all of these factors into consideration, it is likely that the concentrations of PRL or GH we used and found effective in producing cavernous smooth muscle contraction were within the range of clinically relevant hyperprolactinemia or GH excess.

Thus we have demonstrated potent action of PRL and GH in causing cavernous smooth muscle contraction and inhibiting penile erection. On the molar basis, these effects are roughly equipotent to those of noradrenaline, [15,16] a widely accepted inhibitory neurotransmitter in the cavernous tissue. We are not aware of any other naturally occurring bioactive substance of peptidic nature with such a potent antierectile activity as demonstrated for PRL and GH in our current study. A certain type of prostaglandin is also known to cause cavernous contraction [17]

and apparently appears to mediate partially the cavernous contraction caused by PRL in our experiments. However, prostaglandin by itself probably is not as potent as GH or PRL in producing the cavernous contraction in view of the relatively weak inhibitory activity reported for prostaglandins. [17]

Although a physiologic inhibitory role can clearly be assigned to noradrenaline, it is unclear whether PRL or GH would somehow participate in physiologic regulation of the penile function, such as induction of the detumescence phase. With regard to PRL, however, this possibility may be unlikely since administration of bromocriptine to patients with normal serum PRL concentrations does not appear to augment potency nor prolong the duration of tumescence, although it clearly causes infranormal levels of PRL. [18,19] Probably GH and PRL are of only pathologic significance for penile erectile function as opposed to nitric oxide, [20] vasoactive intestinal polypeptide [21,22] and noradrenaline, for which positive and negative physiologic roles have been well established.

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